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<p>(21) International Application Number: PCT/US92/09306</p> <p>(22) International Filing Date: 30 October 1992 (30.10.92)</p> <p>(30) Priority data: 786,384 1 November 1991 (01.11.91) US</p> <p>(71) Applicant: CULTURE TECHNOLOGY, INC. [US/US]: 4911 Van Nuys Blvd., #104, Sherman Oaks, CA 91403 (US).</p> <p>(72) Inventor: NYCZAK, Ewa ; 711 Rome Drive, Los Angeles, CA 90065 (US).</p> <p>(74) Agents: OLDENKAMP, David, J. et al.; Poms, Smith, Lande &amp; Rose, 2121 Avenue of the Stars, Suite 1400, Los Angeles, CA 90067 (US).</p>		<p>(81) Designated States: CA, JP, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, SE).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
<p>(54) Title: CULTURED SKIN GRAFT CARRIER</p> <div data-bbox="393 1071 1250 1491"> </div> <p>(57) Abstract</p> <p>A transportable cultured skin graft (10) which includes a skin layer (12) which is releasably attached to a supporting layer of hydrophilic polymer (18). The hydrophilic polymer layer (18) is sufficiently tacky to hold and support the skin layer (12) during transportation. The hydrophilic polymer support layer (18) is removed after application of the skin layer (12) to the wound site or donor. Storable skin graft assemblies (20) are also disclosed in which the cultured skin graft (22) is sandwiched between hydrophilic polymer layers (24, 26). This sandwich assembly (20) provides protection for the cultured skin (22) during cryopreservation or other storage procedure.</p>		

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## CULTURED SKIN GRAFT CARRIER

### BACKGROUND OF THE INVENTION

#### 1. Field of the Invention

The present invention relates generally to the transportation, use and storage of cultured  
5 keratinocytes (skin grafts). More particularly, the present invention relates to the backing or support layers which are used to protect and support the cultured skin graft during transportation and/or storage.

#### 10 2. Description of Related Art

Cultured keratinocytes, in the form of either allografts or autografts, are widely used to treat burn patients. The most common method for culturing keratinocytes involves seeding them into a suitable  
15 growth media which is located in a culture flask or petri dish. The cells are grown in vitro to confluency to form tissue which becomes attached to the bottom surface of the flask or dish. After reaching confluency, the cultured skin is detached from the flask  
20 or dish and immediately transported to the operating room or stored for future use.

It is important that the cultured skin graft is adequately supported and protected to prevent damage during transport and storage. Surgical gauze is one  
25 material which has been widely used as a protective backing and support layer. The gauze layer is first coated with petroleum jelly and cut so that it is slightly smaller than the cultured skin graft layer. The gauze layer is then floated in the culture medium  
30 directly over the skin graft layer. The edges of the skin graft layer are folded up over the gauze and clipped or glued in place. The gauze-skin graft

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assembly is then ready to be transported to the operating room for application to the patient. If not needed immediately, the gauze-skin graft assembly is rolled up and stored for future use.

5        One of the disadvantages of using gauze as a support layer is that it tends to become attached to both the skin graft and the patients own tissue. As a result, it is many times quite difficult to remove the gauze from the patient without causing some pain and  
10 possible tissue damage. Another disadvantage of gauze is that it is relatively inelastic. This presents problems when applying the gauze-skin graft assembly to uneven bodily surfaces. It would be desirable to provide a new type of support layer which reduces the  
15 problems associated with the use of gauze and similar materials as a support layer.

Collagen is many times used as a feeder layer to enhance growth of the keratinocyte culture. The resulting skin graft includes an integral layer of  
20 collagen. The collagen layer cannot tolerate freezing temperatures and usually is damaged during low temperature storage of the cultured skin graft. Gauze does not provide adequate protection when used as a support layer to prevent the collagen from being damaged  
25 during low temperature storage. Accordingly, it would be desirable to provide a support layer which protects the collagen layer against damage during low temperature storage of skin grafts.

#### 30        SUMMARY OF THE INVENTION

In accordance with the present invention, transportable and storable cultured skin grafts are provided which solve a number of the problems which are associated with gauze and similar support layers. The  
35 present invention is based upon the discovery that hydrophilic polymers can be advantageously used to support, transport and store cultured skin grafts.

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The cultured skin grafts in accordance with the present invention include a full thickness skin graft which is supported by at least one layer of hydrophilic polymer. The hydrophilic polymer, which may be a hydrogel such as polyvinyl pyrrolidone is attached to the dermal side of the cultured skin layer.

As a feature of the present invention, the hydrophilic support layer can include one or more bioactive agents such as topical medicaments or culturing media. The hydrophilic nature of the hydrogel enhances the ability to incorporate a wide variety of medicaments and water-based culture media into the support layer. As a result, the cultured skin layer is continually nourished during transport. The hydrophilic nature of the support layer also provides a cushioning effect which protects the cultured skin during transport.

Skin grafts supported by the hydrophilic support layer of the present invention have the advantages of a graft with excellent physical support, ease of handling for surgeons and technical staff, and assurance of graft sterility. The grafts do not require surgical clips or any other securing devices. They are also easy to cut to size for placement on a variety of wound types and sizes. Another advantage provided by the present invention is a graft which allows viable cryopreservation of cultured skin tissue which can be shipped to remote locations or banked for later use.

As another feature of the present invention, the skin graft to be supported is grown on a feeder layer such as collagen. The resulting graft includes multiple layers of keratinized epidermis attached to the feeder layer. The top of the multiple layers of epidermis form the epidermal side of the graft while the bottom of the feeder layer forms the dermal side of the graft. The hydrophilic support layer is attached to the dermal side of the skin graft. Hydrophilic polymers such as

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polyvinylpyrrolidone are preferred. The support layer can include one or more bioactive agents consisting of topical medicaments and can also include culture media.

The transportable skin graft can be further  
5 prepared for storage by attaching a protective layer to the dermal side of the skin tissue. This protective layer is also preferably a hydrophilic polymer such as polyvinylpyrrolidone which also may include one or more bioactive agents. The cultured skin graft containing  
10 the protective layer is most suitable for cryopreservation because it protects the collagen layer against low temperature damage.

The present invention also includes a method for preparing a transportable skin graft. The steps of this  
15 method involve providing a model of skin tissue consisting of cultured epidermal keratinocytes, which may or may not be grown on a feeder layer. The dermal side of the skin graft is releasably attached to a hydrophilic polymer support layer to form a  
20 transportable skin graft having an unattached epidermal side. After transport to the treatment site, the epidermal side of the transportable cultured skin graft is applied to the wound.

A method is also provided for preparing a storable  
25 skin graft. This method involves providing a skin graft in the form of cultured epidermal keratinocytes which may or may not be grown on a feeder layer. The skin graft is releasably attached on its dermal side to a hydrophilic polymer support layer. A hydrophilic  
30 polymer protective layer is also releasably attached to the epidermal side of the cultured skin graft to form a storable skin graft. This method further includes the steps of cryopreserving the storable skin graft, thawing the storable skin graft, releasing the protective layer  
35 from the storable skin graft to form a transportable skin graft having an unattached epidermal side, applying the epidermal side of the transportable skin graft to a

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wound or donor site of a subject, and releasing the tissue layer from the hydrophilic polymer support layer.

The above discussed and many other features and attendant advantages of the present invention will become better understood by reference to the following detailed description of the invention when taken in conjunction with the accompanying drawings.

#### BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a diagrammatic side view of a portion of a preferred exemplary transportable skin graft in accordance with the present invention.

FIG. 2 is a diagrammatic side view of a portion of a preferred exemplary storable skin graft in accordance with the present invention.

#### DETAILED DESCRIPTION OF THE INVENTION

The present invention involves the use of one or more hydrophilic layers to support and protect cultured skin grafts during transport and storage. The hydrophilic layers in accordance with the present invention are well suited for use in connection with all types of skin grafts including both autografts and allografts. In addition to providing advantages with respect to the transport and storage of skin grafts, the hydrophilic support layers also provide advantages with respect to the actual application of the skin to the burn or other wound site.

In accordance with the present invention, it was discovered that hydrophilic polymers (i.e. hydrogels) could be substituted for gauze as a skin graft backing or support layer. Hydrogels are a well known group of polymers which are widely available. Polyvinylpyrrolidone is one of the more common hydrophilic polymers and is preferred for use in accordance with the present invention. A number of hydrogels based on polyvinylpyrrolidone are commercially

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available and sold for use as a wound dressing. Nu-Gel® is a preferred commercially available hydrogel. Nu-Gel® is available from Johnson & Johnson Medical Inc. (Arlington, Texas). Nu-Gel® is supplied as a sheet or  
5 layer of a sterile hydrogel formulation of preserved polyvinyl pyrrolidone in water. The gel is supported by a fusible fiber fabric and is protected on both sides by polyethylene film. The Nu-Gel® is typically supplied as 3 1/2" x 3 1/2" or 6" x 6" squares.

10 Although Nu-Gel® is the preferred hydrogel, other similar hydrogels may also be used. Other suitable hydrogels (hydrophilic polymers) include those disclosed in United States Patent Nos. 4,646,730; 4,904,247; and 4,393,048. The contents of these patents are hereby  
15 incorporated by reference. The hydrogels are preferably reinforced with a thin layer of fabric such as the fabric used to reinforce Nu-Gel®.

A preferred exemplary portable skin graft in accordance with the present invention is shown generally  
20 at 10 in FIG. 1. The transportable cultured skin graft 10 includes a skin layer 12 which has an epidermal side 14 and a dermal side 16. The skin graft 12 is grown according to any of the known procedures for culturing keratinocytes to form multiple layers of tissue in  
25 vitro. The keratinocytes may be cultured with or without an underlying feeder layer. The use of a feeder layer is preferred. A suitable feeder layer is collagen which may or may not be cross-linked. Cross-linking of the collagen feeder layer is preferred. The feeder  
30 layer is located on the dermal side of the keratinized tissue and forms the dermal side of the skin graft.

The Nu-Gel® or other suitable hydrophilic polymer support layer 18 is attached to the dermal side 16 of the skin graft 12. The cultured skin graft 12 is  
35 attached to the support layer 18 by lightly pressing the two layers together. The media content of the hydrophilic polymer support layer 18 is maintained to



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provide a tacky surface to which the dermal side 16 of the skin graft layer 12 is releasably bonded. The amount of liquid adsorbed into Nu-Gel®, as commercially supplied, provides a hydrophilic layer with an acceptable degree of tackiness. It is preferred that a small amount of additional media be added to slightly reduce the tackiness.

The degree of tackiness present in Nu-Gel® enables one to attach the support layer 18 to the cultured skin graft 12 without the need of additional clips, or adhesives. The tackiness of the Nu-Gel® layer is sufficient to hold the cultured skin graft 12 in place during transport and storage. However, the cultured skin graft 12 may be easily separated from the Nu-Gel® by peeling the Nu-Gel® away from the skin graft layer 12 or by adding additional amounts of media or physiological solution into the Nu-Gel® in order to reduce tackiness. As previously mentioned, other hydrophilic polymers or hydrogels may be used in place of Nu-Gel® provided that they exhibit the same adhesive qualities and structural characteristics.

The transportable skin graft shown in FIG. 1 is well suited for immediate transport to the operating room for application to the burn patient. When it is desired to store the cultured skin graft for extended periods of time, it is preferred that an additional protective layer be utilized. Referring to FIG. 2, a skin graft 20 is shown which is suitable for storage. The skin graft 20 includes a central cultured skin graft layer 22 which is sandwiched between a lower hydrogel support layer 24 and an upper protective hydrogel layer 26. The skin layer 22 is oriented so that the dermal side 28 is adhered to the lower support layer 24 and the epidermal side 30 is adhered to the upper protective layer 26. The storable cultured skin graft shown in FIG. 2 is basically the same as the transportable cultured skin graft shown in FIG. 1 except for the

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addition of protective layer 26. Protective layer 26 is designed to protect the skin from dehydration and damage during cryopreservation processing.

As mentioned above, Nu-Gel® and other hydrophilic polymer wound dressings are supplied as a hydrogel sandwiched between two polyethylene film protective barriers. In accordance with the present invention, only one of the protective films is removed prior to application of the hydrogel to the skin layer. The polyethylene film is shown at 32 in FIG. 1. In FIG. 2, the polyethylene film or protective layer 26 is shown at 34 and the polyethylene film or protective layer for support layer 24 is shown at 36. Other polymers may be used in place of polyethylene provided that they exhibit the same properties of polyethylene including impermeability to moisture and flexibility.

The polyethylene barriers 32, 34 and 36 are desirable since they provide added protection to the cultured skin graft and prevent dehydration of the hydrogel. The use of the outer polyethylene layers 34 and 36 is especially important when storing the skin graft to prevent dehydration and damage. The transportable skin graft 10 shown in FIG. 1 is suitable for transporting the cultured skin graft 12 for relatively short periods of time. When extended transport of the cultured skin graft is required, it is preferred that an additional protective layer of hydrogel be applied as shown in FIG. 2. Upon reaching its destination, the additional protective layer of hydrogel can easily be removed prior to application of the skin to the patient.

The continual intimate contact between the hydrophilic polymer support layer and cultured skin graft provides a convenient means for introducing medicaments, culture media and other bioactive agents into contact with the cultured skin graft. For example, culture media used to nourish and sustain the cultured

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skin graft layer may be absorbed directly into the underlying hydrogel support layer. In addition, medicaments, bacteriological agents, etc. may also be introduced into the hydrogel layer as an aqueous solution. Any of the culture media ingredients, medicaments or other bioactive agents conventionally used in the growth and maintenance of keratinocytes may be used. It is only necessary that the particular agent be water soluble so that it can be taken up by the hydrogel layer for intimate contact with the skin layer.

The protective layer which is attached to the cultured skin graft prior to storage or long-distance transportation can also be treated with aqueous solutions of culture media, medicaments and other bioactive agents. If desired, the lower support layer may include one type of ingredient, such as culture media while the protective layer may include some other type of medicament or bioactive agent which helps to preserve the skin layer during the freezing and thawing associated with long term storage and preservation.

After application to the wound site, the hydrophilic polymer support layer can be removed or left in place for a short period as a wound dressing. The hydrophilic polymer support layer should not be left on the wound for extended periods of time due to possible damage to the skin graft. If any problems are experienced in releasing the support layer from the cultured skin graft, it is preferred that the hydrogel be treated with a small amount of physiological solution in order to reduce tackiness. Only the amount of liquid necessary to allow the support layer to be easily removed from the skin graft should be added to the hydrogel.

The hydrogel layers in accordance with the present invention are used in the same manner as gauze and other prior skin graft support materials. After the skin cells are cultured to confluency in accordance with any

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of the well known culturing procedures, the cultured skin layer is disassociated from the underlying flask surface and floated in the supporting culture media. The skin graft is then removed from the culture media and placed on a suitably sized piece of Nu-Gel® or other hydrogel layer. Preferably, the surface area of the hydrogel layer will be slightly larger than the surface area of the skin graft. Once the cultured skin graft is placed on the hydrogel, it is covered with a transfer media in an amount sufficient to be easily absorbed by the gel. For a 10 x 10 square centimeter section of gel, approximately 5 milliliters of transfer media is sufficient to nourish and maintain the skin layer while not significantly reducing tackiness and adherence of the skin to the gel. A variety of transfer medias and their formulations are well known and commercially available. A preferred exemplary media is available from Flow Laboratories (Maclean, Virginia). After treatment with the transferred media, the cultured skin graft and supporting hydrogel layer are then ready for transport to the operating room for application to the wound or donor site.

The inherent elasticity at cultured skin grafts makes them well suited for applying to uneven surfaces. The cultured skin graft, after being detached from the hydrogel support layer, may be gently stretched to accommodate a wide variety of contoured surfaces. When it is desired to release the hydrogel from the cultured skin graft, additional amounts of transfer media, culture media or other aqueous based solution is added to the support hydrogel. Although not essential, the addition of media reduces the tackiness of the hydrogel and makes it easier to remove.

The procedure for storing cultured skin grafts is the same as for preparing the transportable skin graft except that the additional protective hydrogel layer is added. Culture media is then absorbed into both layers

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and the sandwiched assembly frozen according to any conventional cryopreservation procedure. For sections of gel on the order of 10 x 10 square centimeters, a total of approximately 5 milliliters of culture media is added to the hydrogel layers. After equilibration, the sandwich assembly is packaged in a foil pouch and frozen at a rate of one degree per minute and stored in liquid nitrogen.

Having thus described exemplary embodiments of the present invention, it should be noted by those skilled in the art that the disclosures herein are exemplary only and that various other alternatives, adaptations and modifications may be made within the scope of the present invention. Accordingly, the present invention is not limited to the specific embodiments as illustrated herein, but is only limited by the following claims.

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CLAIMSWhat is claimed is:

1. A transportable skin graft comprising:  
a skin graft having a dermal side and an epidermal side; and  
a support layer comprising a hydrophilic polymer, said support layer being attached to said dermal side of said skin graft.
2. A transportable skin graft according to Claim 1 wherein said hydrophilic support polymer comprises polyvinylpyrrolidone.
3. A transportable skin graft according to Claim 1 wherein said support layer includes fiber reinforcement.
4. A transportable skin graft according to Claim 1 wherein said support layer includes a barrier layer on the side of said support layer opposite said skin graft.
5. A transportable skin graft according to Claim 1 wherein said support layer includes one or more bioactive agents.
6. A transportable skin graft according to Claim 1 wherein said skin graft comprises a keratinized tissue layer and a feeder layer.
7. A transportable skin graft according to Claim 1 further comprising a protective layer comprising a hydrophilic polymer, said protective layer being attached to said epidermal side of said skin graft.

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8. A transportable skin graft according to Claim 7 wherein said protective layer includes a barrier layer on the side of said protective layer opposite said skin graft.

9. A transportable skin graft according to Claim 7 wherein said protective layer comprises polyvinylpyrrolidone.

10. The transportable skin graft according to Claim 9 wherein said protective layer includes fiber reinforcement.

11. A transportable skin graft according to Claim 7 wherein said protective layer includes one or more bioactive agents.

12. A transportable skin graft according to Claim 11 wherein said bioactive agent is culture media.

13. A method for preparing a transportable skin graft comprising the steps of:

providing cultured keratinocytes in the form of a multiple layered tissue having a dermal side and an  
5 epidermal side;

releasably attaching said dermal side of said layer of tissue to a hydrophilic polymer support layer to form a transportable skin graft.

14. A method according to Claim 13 further including the steps of applying the epidermal side of said transportable skin graft to a graft site.

15. A method according to Claim 14 further including the step of removing said support layer from said skin graft.

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16. A method according to Claim 13 wherein said hydrophilic polymer support layer comprises polyvinylpyrrolidone.

17. A method according to Claim 13 wherein said hydrophilic polymer support layer includes fiber reinforcement.

18. A method according to Claim 13 including the further step of adding one or more bioactive agents to said support layer.

19. A method for preparing a storable skin graft comprising the steps of:

providing cultured keratinocytes in the form of a multiple layered tissue having a dermal side and an  
5 epidermal side;

releasably attaching the dermal side of said skin layer to a hydrophilic polymer support layer;

releasably attaching the epidermal side of said skin layer to a hydrophilic polymer protective  
10 layer support layer to form a storable skin graft.

20. The method of Claim 19 further including the step of cryopreserving said storable skin graft.

21. A method according to Claim 19 wherein said support and protective layers comprise polyvinylpyrrolidone.

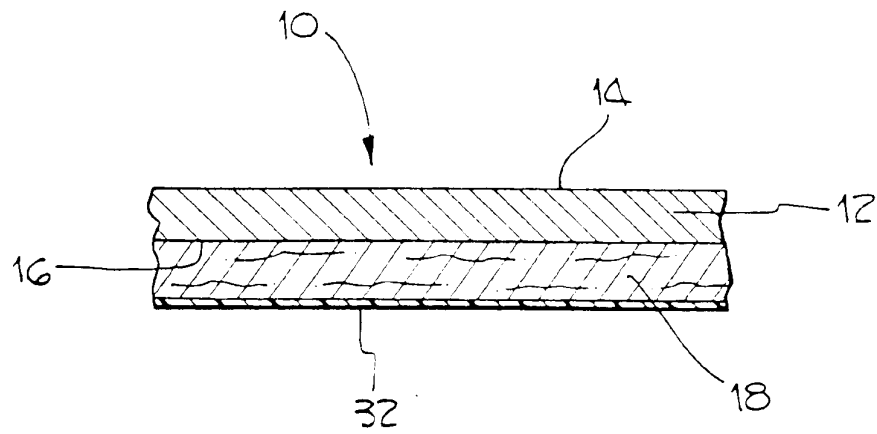
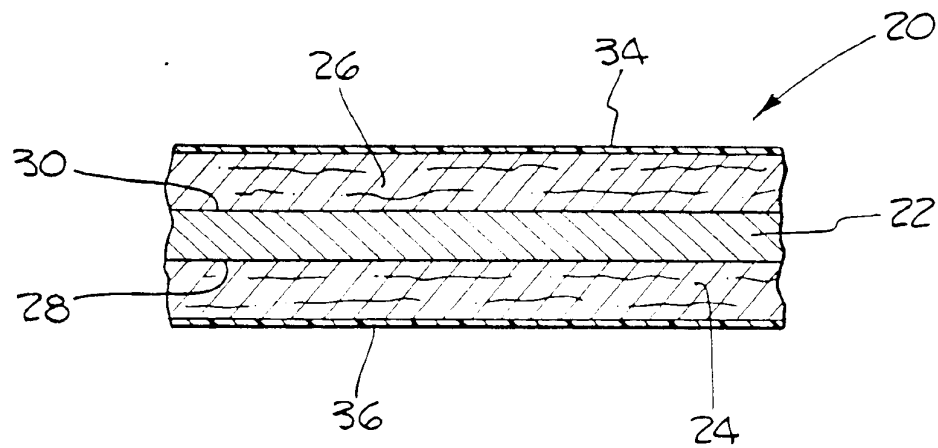
22. A method according to Claim 19 wherein said support and protective layers include fiber reinforcement.



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23. A method according to Claim 19 including the additional step of adding one or more bioactive agents to at least one of said support or protective layers.

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*Fig. 1.**Fig. 2.*

<b>A. CLASSIFICATION OF SUBJECT MATTER</b>														
IPC(5) : A61F 13/00 US CL : 424/443														
According to International Patent Classification (IPC) or to both national classification and IPC														
<b>B. FIELDS SEARCHED</b>														
Minimum documentation searched (classification system followed by classification symbols)														
U.S. : 424/443; 435/240.23; 424/574; 523/105, 111														
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched														
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)														
APS - search terms: artificial skin, keratinocytes, skin graft, polyvinylpyrrolidone, nugel, collagen.														
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>														
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.												
Y	US, A, 4,888,291 (BARRANDON ET AL) 19 DECEMBER 1989; See claim 3.	1-23												
Y	US, A, 5,000,963 (HEFTON) 19 MARCH 1991 See column 5, line 66 through column 6, line 6.	1-23												
Y	US, A, 5,040,677 (TUBO ET AL) 20 AUGUST 1991 See entire document.	1-23												
A	US, A, 4,304,866 (GREEN ET AL) 08 DECEMBER 1981; See entire document.	1-23												
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.														
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Date of the actual completion of the international search 29 DECEMBER 1992		Date of mailing of the international search report 17 MAR 1993												
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